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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/551,977

Filing Date: April 14, 2000

Appellent(s): POLO ET AL.

ROBINS & PASTERNAK LLP

For Appellant

## EXAMINER'S ANSWER

This is in response to the appeal brief filed JULY 18, 2005.

A statement identifying the real party in interest is contained in the brief.

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

***(2) Related Appeals and Interferences***

***(3) Status of Claims***

The statement of the status of the claims contained in the brief is correct.

***(4) Status of Amendments After Final***

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

***(5) Summary of Invention***

The summary of invention contained in the brief is correct.

***(6) Issues***

The appellant's statement of the issues in the brief is correct.

***(7) Grouping of Claims***

The rejection of claims 17, 19, 21-23 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).***(8) Claims Appealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

***(9) Prior Art of Record***

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

*(10) Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 19, 21-23 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application filed, had possession of the claimed invention. In the instant case, the specification only teach that they have isolated a mutated Sindbis virus vector that is able to infect human dendritic cells (DC), which comprises a substantive mutation at amino acid residue 160 of Gly for Glu of said Sindbis virus (SIN) E2 protein. However, Applicants do not have a possession for having any other alphavirus vector made by a mutated alphavirus with a mutation corresponding to the amino acid residue 158-162 of E2 protein of SIN, which is able to infect human DC (Office Action mailed on June 03, 2004).

Whether the appellants have the possession of claimed invention, the factors related to 1). Level of skill in the art; 2). Method of making it; 3). Complete or partial structure; 4). Physical and/or biological properties; and 5). Correlation between structure and function that are considered set forth bellow:

Alphaviruses are a group of arthropod-bone viruses in Togaviridae family wildly distributed in the animal kingdom and human being and persisted in nature through a particular life circle from a mosquito to vertebrate. The family of the viruses comprises twenty-six known virus and virus serotype as well as many isolates. While all alphaviruses are genetically, structurally and serologically related as they all comprise two to three structural envelope proteins (E1- E3) and four non-structural proteins (NPS1-4), the genomes of alphaviruses

consisting of a single molecule of linear, positive-sense, single-stranded RNA vary in size from 9.7-11.8 kb. For examples, most alphaviruses comprise E1 and E2 envelope proteins with molecular weights from 45,000-58,000. Some alphaviruses have a third envelope protein E3 with molecular weight about 10,000. Moreover, alphaviruse is a RNA virus; it mutates from one isolate to another. The genetic codes and sizes of the E2 glycoproteins change with different alphaviruses or even among the different isolates too. Therefore, even the procedure of making E2 glycoprotein mutation and assay of testing human dendritic cell infectivity are all well known in the art, they make no reference for a mutated alphavirus still in question. In fact, up-to-date, only one paper has been published by the appellants' group post filling date (J. Virol. (December 2000, Vol. 74, pp. 11849-11857), which reports that only one single substitutive mutation of Gly for Glu at 160 of SIN E2 changes the SIN to become human DC tropic virus.

The broad scope of the claimed invention reads on any other alphavirus vector made by mutated alphaviruses with a mutation corresponding to the amino acid residues 158-162 of SIN E2, which is able to infect human DC. As described above, alphaviruses have many members and isolates, which vary in sizes and genetic codes, the precise mutations in term of amino acid substitution and position for each alphavirus are probably not the same compared to the SIN E2. For example, the amino acid sequences of SIN E2 proteins vary among the different isolates (Accessory number AAA96973, AAO33325, AAO33347 and AAC83379), which is also very much different from the E2 protein of other alphavirus, such as Semliki Forest virus (Accessory number NP 819006). The specification does not teach which position correspond to the amino acid residue 158-160 of SIN E2 is important for the substitutive mutation, and which kind of amino acid should be used for the substitution for any or all claimed alphavirus. The specification lacks of teaching any more complete or partial sequence of mutated E2 for all claimed alphaviruses or the physical and/or biological properties of the other mutants except the claimed Sindbit virus. The specification is deficient for describing any correlation between the structure and function for each amino acid residues in the locations from 158 to 162 corresponding to the claimed Sindbis virus except the position 160 with Gly for Glun substitutive mutation. For example, Semliki Forest virus (NP 819006) does not have Glu at position 160 in addition to many other genetic code differences in E2. Therefore, it probably exhibit different biological function caused by its 1$^{st}$ to 4$^{th}$ dimensional or tertiary structure of the protein. While

the technique and sequence are available for making the mutation, they still make no reference for the particular mutated alphavirus in question.

MPEP cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)." In the instant case, there is no any reduction to practice all species of the claimed mutated alphavirus genus that has been referred in application (page 21, lines 5-19); therefore, it concludes that the appellants do not have the possession of all other claimed mutated alphavirus vectors.

Appellants assert in the Appeal Brief that the specification has more than enough of description of all claimed alphavirus mutants and one single species of SIN mutant with mutation of Gly for Glu at position 160 of E2 can be used for represent the claimed genus of all alphavirus mutants having mutant at position(s) corresponding to the amino acid residues from 158 to162 of SIN E2.

The following is the response to the Appellants argument in the appeal brief:

***(11) Response to Argument***

***(a).*** Appellants first assert that the examiner has failed to analyze what is actually claimed, and improperly asserted that a single representative species does not adequately describe the claims. Appellants explain that the claims are drawn to particular alphavirus particles fully described by the specification as filed, and they are relative small genus of recombinant alphvirus particles, namely a recombinant alphavirus particles that infect human dendritic cells and include a mutation in at least 5 specific amino acid residues in their E2 protein not. They are not drawn to any and all recombinant alphavirus particles having any mutation as painted by the examiner.

Appellants' argument has been respectfully considered; however, it is not found persuasive because the examiner does not interpret the claimed invention broadly as any and all

recombinant alphavirus particles having any mutation. Instead, the broad scope is only reasonable interpreted by the examiner as any other isolated alphavirus clone having a mutation at the position corresponding to the amino acid residue at 158-162 of SIN E2 envelope protein that is able to infect human DC (See office action mailed on June 03, 2004, page 4, paragraph 13).

(b). Appellants assert that the claims are more than adequately described by the specification as filed (page 3, line 23 to page 4, lines 8, 19-22, page 5, lines 4-10, page 1, lines 12-13, page 2, lines 8-15, page 32, lines 6-12, and page 21, lines 4-19). Further, Applicants contest that the well-settled case law, e.g. Vas Cath, Inc. v. Mahurkar, 935, F.2d 1557 USPQ2d 1111; In re Wertheim, 191 USPQ 90 (CCPA 1976), and In re Lukach, 169 USPQ 795, 796 (CCPA 1971) teach that requirement in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filling date sought.

Appellants' argument has been respectfully considered; however it is not persuasive. According to MPEP: To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably concluded that the inventor had possession of the claimed invention. The possession of claimed invention can be shown by describing the claimed invention with all of its limitation in the specification including a drawing or description of an actual reduction to practice. The written description may arise in the following situations: a). The claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention; b). The claimed invention as a whole may not adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art; and c). The invention is described solely in terms of a method of its making coupled with its function and there is no described or art recognized correlation or relationship between the structure of the invention and its function etc.

In the instant case, the specification lacks sufficiently description that one skilled in the art would recognize that the appellants had possession of the claimed invention. Alphaviruses are a group of arthropod-bone viruses in Togaviridae family wildly distributed in the animal kingdom and human being, and persisted in nature through a particular life circle from a

mosquito to vertebrate. The family of the viruses comprises twenty-six known virus and virus serotype as well as many isolates. While all alphaviruses are genetically, structurally and serologically related as they all comprises two to three structural envelope proteins E1- E3 and fore non-structural proteins, the genomes consisting of a single molecule of linear, positive-sense, single-stranded RNA vary in size from 9.7-11.8 kb. While the appellants have cited many species or isolates of alphaviruses in the specification (pages 21, lines 5-19), The specification on pages 1-5, 21 and 32 only cites many alphaviruses existed in the art. The description of other alphavirus that may be mutated in E2 and become human dendritice cell tropism is only hypothetically mentioned. In fact, the specification does not adequately description about how other alphavirus is mutated in E2 since they may have different genetic codes, especially in that claimed region. There is not any example teaching how other alphavirus is mutated in E2 and what the activity of such E2 mutant. The family of alphavirus as applicants stated contains many viruses (at least 38 different viruses that applicants cited in the specification for the claimed alphaviruses referred to), it is well known in the art that each of them is different in length and genetic codes, the alignment of each alphavirus with SIN would be different and amino acid residues are not same as SIN E2. The specification does not teach how the homologous and consensus sequence for so many alphaviruses are analyzed compared to the SIN. A person skill in the art would not recognize the appellants having the possession of genus of the mutant alphavirus.

Moreover, the claimed invention as a whole is not adequately described in the specification, the claims invention requires an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. For example, the specification does not teach which position correspond to the amino acid residue 158-160 of Sindbis virus E2 is important for the amino a acid substitutive mutation, and which kind of amino acid should be used for the substitution, such as more acidic or more basic or more neutral amino acid should be used for the substitution. Because this type of mutant is not conventional in the art, a person skill in the art would also not recognize the appellants having the possession of genus of the mutant alphavirus if appellants lack of description the mechanism why the Gly for Glu mutation in position E160 make the virus having such dramatic change.

MPEP also cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)." Apparently, as described above, there is no reduction of practice of claimed invention disclosed in the specification.

Regarding to case law of Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), MPEP cites: "The written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.)" In the current case, while some sequences of alphaviruses and method of testing a virus infection for human dendritic cells are available in the art, the enablement issue is separate from the written description problem, they do not make any reference for the claimed product still in question.

(c). Appellants assert that disclosure of a single species can satisfy the written description requirement.

Appellants argue that the broad scope of claimed invention is reasonable interpretation as any or all recombinant alphavirus particle comprising an alphavirus replicon comprising a heterologous sequence; and an amino acid mutation in its E2 glycoprotein, wherein the mutation in the E2 glycoprotein us in the region corresponding to amino acids 158-162, numbered relatively to wild-type SIN E2 glycoprotein, and further wherein said particle is capable of infecting human dendritic cells, with the proviso that said recombinant alphavirus particle is not derived from ATCC#VR-2526. The specification has referred the alphavirus as many suitable

alphaviruses including Aura virus (ATCCVR-368), Bebaru virus (ATCC VR-600, ATCC VR-1240), Cabassou virus (ATCC VR- 922), Chikungunya virus (ATCC VR-64, ATCC VR-1241), Eastern equine encephalomyelitis virus (ATCC VR-65, ATCC VR-1242), Fort Morgan virus (ATCC VR- 924), Getah virus (ATCC VR-369, ATCC VR-1243), Kyzylagach virus (ATCC VR-927), Mayaro vinzs (ATCC VR-66, ATCC VR-1277), Middleburg virus (ATCC VR-370), Mucambo virus (ATCC VR-580, ATCC VR-1244), Ndumu virus (ATCC VR-371), Pixuna vinzs (ATCC VR-372, ATCC VR-1245), Ross River vinzs (ATCC VR-373, ATCC VR-1246), Semliki Forest virus (ATCC VR-67, ATCC VR-1247), Sindbis virus (ATCC VR-68, ATCC VR-1248; see also CMCC #4640), Tonate virus (ATCC VR- 925), Triniti virus (ATCC VR-469), Una virus (ATCC VR-374), Venezuelan equine encephalomyelitis virus (ATCC VR-69, ATCC VR-923, ATCC VR-1250 ATCC VR-1249, ATCC VR-532), Westem equine encephalomyelitis virus (ATCC VR-70, ATCC VR-1251, ATCC VR-622, ATCC VR-1252), Whataroa virus (ATCC VR-926), and Y-62-33 virus (ATCC VR-375) (See page 21, lines 5-19). The question is whether only one single example of a species, i. e. Sindbit virus, can satisfy the written description requirement for the genus of the claimed recombinant alphavirus particle.

MPEP cites: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i) (C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004)**

**(Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.**

In the instant case, the genus of the alpphavirus contains many members of viruses as appellants cited in the specification. Some of the alphavirus sequences are available in the art, and the technique of testing the mutated alphavirus as a human dendritic cells tropism has been taught in the specification. However, the genomes of alphaviruses are different in lengths (e.g. Sindbit virus (SIN) has 11703 bp, Venezuelan equine encephalitis virus (EEV) has 11444 bp, Semliki forest virus (SF) has 11442 bp, Ross River virus (RR) has 11657 bp). Therefore, sequences of E2 envelope protein vary greatly. The alignment of N-terminal starting regions of the E2 glycoproteins among the all members of alphavirus relative to SIN would not be same too, and the relative positions corresponding to amino acid residues of 158-162 of SIN E2 among different alphaviruses are undefined by the specification and universally accepted or recognized by the state of art. Even if the relative position may be measurable by taking length of times for a person skill in the art, which is only an enablement issue and is separate problem from the written description since the mutations for all other species of the claimed alphaviruses have not bee defined yet. In view large members of the alphaviruses in the art, and their different genetic structures, especially in that claimed region, only one single species of SIN E2 mutation of Gly for Glu at amino acid residue 160 cannot represent all alphaviruses mutant as claimed drafted.

Hence, Appellants will not be deemed to have invented all species of the large family of alphavirus genus if other mutated alphavirus is still in question.

(d). Appellants argue that the Office has not considered Dr. Polo's Declaration filed on 07/28/2003.

The argument has been respectfully considered; however, it is not found persuasive and accurate because the Declaration was not filed in response to the written description and

appellants did not ask the examiner to consider the Declaration prior to the current appeal brief was filed.

i). The Declaration by Dr. Polo was filed On July 28, 2003, in response to the 112 1st paragraph enablement rejection made in Office Action mailed on January 27, 2003. No written description rejection was made in that office Action.

ii). In the office Action mailed on September 25, 2003, the Examiner had fully considered the Declaration; the enablement issue was withdrawn after considering the Dr. Polo's Declaration.

iii). In the Office Action mailed on June 30, 2004, the written description rejection was made after applicants filed RCE.

iv). In the response filed on September 07, 2004, appellants only made an argument to the enablement rejection and ignored the written description rejection.

v). In the Office Action mailed on November 30, 2004, the examiner reminded the appellants that the traversal of the written description rejection lacks any argument presented in the response.

vi). The response filed on May 26, 2005, Appellants present argument for the written description rejection. However, Appellants did not argue that the examiner should consider Dr. Polo's Declaration, and Applicants did not use any evidence presented by Dr. Polo's Declaration in the argument.

vii). The advisory Action was mailed on June 26, 2005. The rejection on enablement was maintained.

viii). Appellants filed the current Appeal brief on July 18, 2005 and asserted that examiner did not consider the Declaration.

Apparently, Appellants did not ask the examiner to considered Dr. Polo's Declaration. Appellants also did not response to the written description in the Office Action mailed on June 30, 2004 with the evidence brought by Dr. Polo's Declaration prior to the current Appeal Brief.

To be on the record, the following is the examiner's answer in response to appellants request for the consideration of Dr. Polo's Declaration.

Dr. Polo stated in the Declaration that 1) at the time of filling, both nucleotide and amino acid sequence of E2 proteins of many alphavirues were known and published. Moreover, even there is any unknown sequence, the person skill in the art is able to get it using conventional methods; 2). In light of the teaching of the specification, it would have been a routine for a typical scientist to mutate one or more of a amino acid residue(s) corresponding to residues 158-162 of E2; 3). to produce the alphavirus particle; and 4). to test the ability of a mutant alphavirus infectivity for human dendritic cells.

Dr. Polo's Declaration has been respectfully considered; however, it isn't persuasive to overcome the enablement rejection. Because apparently, the argument brought by Dr. Polo only answer that the methods of making E2 mutation for an alphavirus and testing the infectivity of the mutant to human dendritic cells infectivity are available or approachable.

MPEP cites: "The written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.)" . MPEP also cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)."

As discussed above, there are many viruses in the genus of alphavirus family, Appellants will not be deemed to have invented species sufficient to constitute the large family of genus virus by virtue of only disclosing a single species of SIN mutant at only one single amino acid residue 160. In view of many alphaviruses with different lengths for their genetic codes in the

art, the exactly position(s) corresponding to the amino acid residues 158-162 of the claimed SIN E2 varies greatly and there is not reduction of practicing the claimed other species of alphavirus mutant by appellants. Therefore, the known sequences and available technique still make no reference to a non-isolated alphavirus mutant in question. Therefore, the Declaration can only overcome the enablement rejection, but it is not insufficient to overcome the written description rejection.

For the above reasons, it is believed that the rejection should be sustained.

**(12) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,
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